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Clinical Study

Brain tumor masquerading as stroke

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Summary

Discriminating brain tumor from stroke in patients presenting with acute focal neurologic signs and symptoms is crucial to avoid improper treatment, or delay correct treatment of the brain tumor patient. Data from the era before computed tomography (CT) suggests that 3% of patients with brain tumors are initially thought to have had a stroke. Our goal was to see if this has improved in the CT era. We reviewed hospital charts of all patients admitted to the Johns Hopkins Hospital with a brain tumor during a one year period. Eleven (4.9%) of the 224 patients discharged with a diagnosis of brain tumor were initially thought to have had a stroke. Seven had primary brain tumors and 4 had metastatic tumors. Patients who were originally misdiagnosed were significantly older ($p = 0.01$) and more likely to have a Glioblastoma Multiforme ($p = 0.04$) than those correctly diagnosed. Eighty-two percent of those misdiagnosed had no prior history of cancer compared to 59% of patients correctly diagnosed. Distinguishing the acute presentation of brain tumor and stroke remains an important diagnostic consideration. Physicians should recognize that while CT is frequently employed for acute neurologic deficits to exclude intracranial hemorrhage, CT may not be sufficient to exclude brain tumor. A prospective study is needed to confirm these findings.

Introduction

Patients with brain tumor may initially present with acute focal neurologic symptoms and signs that mimic stroke. Prompt diagnosis of central nervous system mass lesions in these patients is necessary to avoid treatment with dangerous drugs such as thrombolytic therapy, and to initiate anti-tumor therapies expeditiously. The difficulty in distinguishing brain tumor and stroke has been recognized for some time. In 1926, Elsberg and Globus [1] identified 37 cases of pathologically proven brain tumor which presented with acute stroke-like events. Others have documented that even benign neoplasms such as meningioma can present with acute neurologic events [2,3].

The advent of computed tomography (CT) and magnetic resonance imaging (MRI) of the brain has revolutionized the evaluation of patients with cerebral neoplasms. Similarly, the evaluation of all presumed acute stroke patients as candidates for thrombolytic therapy involves careful reading of a non-contrast CT scan to exclude hemorrhage and mass lesions [4,5]. We sought to determine whether in the age of modern imaging our ability to distinguish between brain tumor and stroke has improved compared to the pre-CT era.

Data from the pre-CT era suggests that from one to three percent of brain tumor patients were initially thought to have had a stroke [6,7]. We reviewed the cases of all patients presenting or referred to a large, tertiary care medical center with a diagnosis of brain tumor over one year and determined whether their initial presentation was misconstrued to be stroke.

Methods

We used ICD-9 codes 191, 192.0, 192.1, 198.3, 198.4, 225, 237.5, 237.6, 239.6, 239.7 [8] to identify all patients with a diagnosis of benign or malignant brain tumor discharged from the Johns Hopkins Hospital (JHH) from October 1991 through September 1992.

Our search in the hospital's Computer Information System allowed us to ascertain patients with a diagnosis of brain tumor as one of the principal five discharge diagnoses. We limited our search to subjects age 21 and over. Medical records were reviewed on all patients by the study neurologist (L.B.M.).

Patient information was obtained on gender, age at presentation, brain tumor diagnosis, presenting symptoms and the initial diagnosis and impression of the first attending physician evaluating the patient's neurologic symptoms. To strive for objectivity subjects were only considered to have been misdiagnosed if the original attending physician's primary diagnosis specified: 'stroke, CVA, cerebrovascular disease, TIA, transient ischemic attack, vascular event, embolus, thrombus.' Cases of patients who were initially thought to have had a stroke were abstracted. Where available, imaging studies of these patients were evaluated.

Frequency distributions of correct brain tumor and incorrect stroke diagnoses among 224 brain tumor cases are reported by age, gender, history of cancer, tumor type, and principal diagnosis and principal presenting neurologic symptom. Associations between incorrect diagnosis and each of these characteristics are summarized by odds ratios computed from 2×2 contingency tables comparing the odds of an incorrect diagnosis to the odds of a correct diagnosis for each characteristic. As a measure of association, the odds ratio can range from zero to infinity. When the odds ratio is one, there is no association between the characteristic and incorrect diagnosis. When the odds ratio is greater than one, incorrect diagnosis is more likely to occur among those with the characteristic than among those without the characteristic. When the odds ratio is less than one, incorrect diagnosis is less likely to occur among those with the characteristic than among those without the characteristic [9].

Estimates of the odds ratios, significance tests and 95 percent confidence intervals were computed using statistical software for exact non-parametric inference. Significance probabilities and exact confidence intervals were computed using conditional exact statistical methods for independent binomial samples. All computations were performed using the commercial software program, StatXact 3 for Windows [10].

Results

The ICD-9 search of all patients discharged during the one year study period with a diagnosis of brain tumor listed as one of the five principal discharge diagnoses yielded a total of 271 cases. On review of each case the study neurologist (L.B.M.) determined that 224 of the 271 (82.7%) cases actually had a brain tumor. Nearly all of the 47 miscoded discharge diagnoses had metastatic disease of the spine.

Of the 224 brain tumor patients 11 were initially thought to have had a stroke or 4.9% (95% C.I. 2.5–8.6%). Insufficient information on initial presentation could be gleaned on seven of the 224 patients (3.1%). Table 1 lists the brain tumor discharge diagnoses. All patients had either CT or MRI. Nine of the 11 misdiagnosed patients had initial CT and two of the 11 had initial MRI. Approximately half (6/11) of the misdiagnosed cases were glioblastoma multiforme (GBM) whereas about a fifth (45/206) of the correctly diagnosed cases had a GBM (Table 1).

Table 2 provides odds ratios as a measure of association between the incidence of an initial error in diagnosis and selected baseline characteristics of the patients. Age greater than 65 years and GBM both have significantly ($p < 0.05$) elevated associations with incorrect diagnoses. All 11 of the initial incorrect diagnoses were among patients between 62 and 77 years of age. Elevated odds ratios for incorrect diagnosis were also found for patients with colon cancer, adenocarcinoma with primary tumors of unknown origin, and lymphoma. These associations are inconclusive due to the small number of cases ($n < 7$) in each of these categories (Table 1). Patients with a prior history

Table 1. Distribution of initial diagnosis stratified by tumor type

	Initial diagnosis			
Tumor diagnosis	Stroke	Tumor	Unknown	Total
GBM[1]	6	45	3	54
Other glioma	0	40	0	40
Adeno unknown primary	2	4	1	6
Colon	1	2	0	3
Lung cancer	1	47	1	49
Lymphoma	1	7	0	8
Breast cancer	0	15	0	15
Head and neck	0	3	1	4
Medulloblastoma	0	3	0	3
Melanoma	0	3	1	3
Meningioma	0	3	0	3
Renal cell	0	5	0	5
Schwannoma	0	9	0	9
Other (2 patients or less)	0	18	0	18
Total	11	206	7	224

[1]glioblastoma multiforme.

Table 2. Odds ratios[1] (and 95% confidence intervals) of initial stroke diagnosis among 217 brain tumor cases stratified by age, gender, cancer history, and tumor type

Factor	Odds ratio	*p*-value[2]	95% confidence interval
age >65 years	6.63	0.01	1.58–32.00
Male	1.05	1.00	0.25–4.29
Cancer history	0.33	0.25	0.03–1.66
Glioblastoma multiforme	4.29	0.04	1.03–18.50
Adeno unknown primary	11.22	0.06	0.88–88.73
Colon	20.50	0.20	0.24–>99.00
Lung cancer	0.34	0.52	0.01–2.50
Lymphoma	2.84	0.69	0.06–25.88

[1]Odds ratios computed comparing the odds of stroke diagnosis with the factor present vs. odds of stroke diagnosis with the factor absent.
[2]Significance level test of the null hypothesis Ho: Odds ratio $= 1$ vs. the alternative hypothesis AH: Odds ratio $\neq 1$.

Table 3. Distribution of initial diagnosis stratified by presenting neurologic symptoms

	Initial diagnosis			
Presenting symptom	Stroke	Tumor	Unknown	Total
Seizure	3	57	1	61
Long tract symptoms	3	24	0	27
Headache	2	40	1	43
Vision change	2	7	0	9
Aphasia	1	5	1	7
Abnormal gait	0	2	0	2
Altered mental state	0	21	1	22
Ataxia	0	9	0	9
Hearing loss or tinnitus	0	6	2	8
Cranial nerve damage	0	10	0	10
Vertigo	0	5	0	5
Incidental CT findings[1]	0	16	0	16
Other	0	4	1	5
Total	11	206	7	224

[1]Patients with known systemic malignancy undergoing head CT for clinical staging purposes.

Table 4. Odds ratios[1] (and 95% confidence intervals) of initial stroke diagnosis among 217 brain tumor cases stratified by presenting neurologic symptoms

Presenting symptom	Odds ratio	*p*-value[2]	95% confidence interval
Long tract symptoms	2.84	0.29	0.45–12.84
Seizure(s)	0.98	1.00	0.16–4.27
Vision change	6.32	0.14	0.55–39.84
Headache	0.92	1.00	0.09–4.71
Aphasia	4.02	0.54	0.08–40.91

[1]Odds ratios computed comparing the odds of stroke diagnosis with the symptom being present to the odds of stroke diagnosis with the symptom being absent.
[2]Significance level test of the null hypothesis Ho: Odds ratio $= 1$ vs. the alternative hypothesis AH: Odds ratio $\neq 1$.

of cancer, particularly lung cancer, before neurologic presentation were less likely to be incorrectly diagnosed as stroke than their counterparts. The data suggest no association of incorrect diagnosis with gender.

The distribution of presenting neurologic symptoms is given in Table 3. Only one principal presenting neurological symptom was recorded for each patient. Seizures, headache and long tract symptoms (focal weakness and numbness) were the most common presenting symptoms in the correctly diagnosed group; whereas change in vision, aphasia and long tract symptoms were the most common presenting symptoms in the group mistaken for stroke.

The associations (odds ratios) between incorrect diagnosis and presenting neurologic symptoms are summarized in Table 4. Elevated odds ratios were found for vision change, aphasia and long tract symptoms, while seizures and headache were found with about equal frequency in the two groups. Although none of the odds ratios are statistically significant, it should be kept in mind that the number of incorrect diagnoses limits the statistical power of the study to less than 50% to detect two fold elevations of odds ratios.

Figure 1 shows imaging from a representative case. The patient was a 63 year old woman who presented with acute onset of right hand clumsiness, expressive aphasia and right upper extremity weakness. Her symptoms resolved completely over 24 h. A CT without contrast (a) suggested sulcal effacement. The patient was presumptively diagnosed with a stroke. She underwent carotid duplex, cerebral angiography and echocardiography. All were normal. Two weeks later her symptoms recurred and an MRI was obtained (b). Biopsy of the lesion revealed a GBM.

Discussion

The importance of correctly distinguishing between brain tumor and stroke in patients with acute neurologic syndromes is critical. With the consideration of

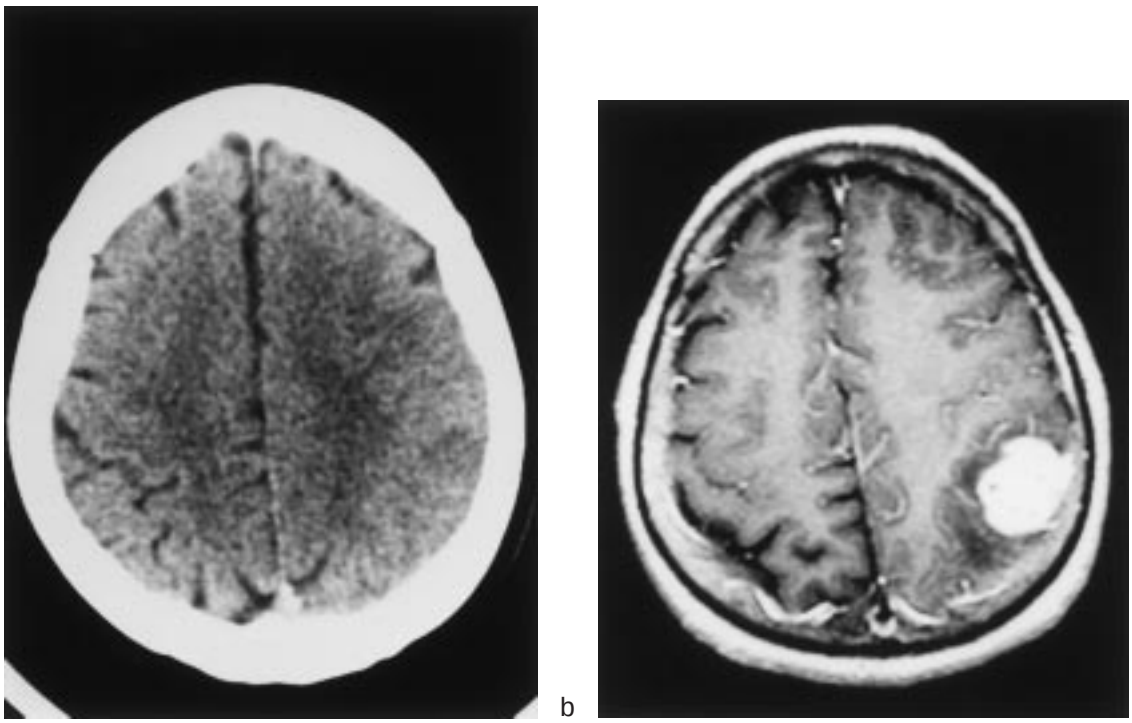

Figure 1. (a) Non-contrast head CT of a 63 year old woman with acute onset of right arm weakness and aphasia. Note subtle left parietal sulcal effacement. (b) Gadolinium enhanced T1 weighted brain MRI scan obtained two weeks later reveals an enhancing left parietal lobe mass lesion.

rt-PA therapy [5] for acute ischemic stroke within three hours of symptom onset, quick diagnostic decisions are imperative. Patients with brain tumor should not be given thrombolytics. As other clinical trials progress for acute stroke, physicians in the emergency department must be able to differentiate brain tumor and stroke immediately.

Furthermore, delaying the diagnosis of brain tumor may allow further spread of the neoplasm and cause increased morbidity and mortality. Indeed, we know that early surgical excision of solitary metastases improves survival and quality of life [11,12]. The question remains, what is the best method to exclude brain tumor as a diagnosis of patients who present to the emergency room with an acute neurologic process?

Data from the pre-CT era suggests that approximately three percent of patients initially diagnosed with stroke actually had a brain tumor [7]. Groch et al. [6] reviewed 303 patients in New York with initial diagnoses of stroke. Of these, four (1.3%) were later found to be neoplastic. These authors do not comment on whether diagnoses were confirmed pathologically. Carter [13] found 10 brain tumors in 289 patients initially diagnosed with stroke (3.5%).

We can compare these results to data obtained with the use of CT imaging. The UK-TIA study group [14] studied 2449 patients with acute, transient neurologic symptoms. Eleven of these patients (0.45%) were later found to have a brain tumor. Five had gliomas and five meningiomas. In three patients subsequent review of CT imaging confirmed a 'negative' CT. The authors do not discuss whether patients with a previous history of systemic or CNS malignancy was an exclusion for the trial, but conclude that four main factors identify patients with brain tumor: focal jerking or shaking, pure sensory phenomena, loss of consciousness, and isolated aphasia or speech arrest. If we apply this criteria to our 11 misdiagnosed patients we would only have detected three of the 11 brain tumors.

Although classical teaching suggests that brain tumor presents more indolently than vascular events, the mechanism of acute 'tumor attacks' has received much speculation [15–21]. Plausible explanations include: post-seizure (Todd's) paralysis, acute

intracranial pressure changes and consequent reduced cerebral blood flow, vascular steal phenomena, acute hemorrhage, vascular compression and resultant infarction, and tumor embolus. All types of stroke syndromes can be mimicked by mass lesions including lacunar disease [22]. On CT scanning brain tumor may be distinguished from stroke by the presence of multiple lesions, mass effect, lack of a vascular distribution and contrast enhancement. However, some overlap does exist.

Of the 224 patients with brain tumor referred to the JHH during a one year period, 11 or 4.9%, were initially misdiagnosed as stroke. These patients tended to be older, have primary brain tumors, and present with long-tract symptoms. It was also more likely for these patients to have no prior history of cancer. This study determined that a little over half of brain tumors seen at JHH were primary in origin. This is consistent with previous reports [23] and suggests that referral bias for primary tumors may be less than expected. Furthermore, seizure was by far the most common presenting symptom of brain tumor patients in this study. Two recent reports suggest that brain tumor is a relatively common etiology of adult new-onset seizures [24,25]. In both studies approximately 10% of new-onset seizures are a result of brain tumor. Headache, previously thought to be the overwhelming most common symptom of tumor was found to be the most prominent symptom in only 42 (19%) of the patients in this study. This is comparable to recent reports [26].

Our study, however, is subject to bias. Most importantly, the number of initial misdiagnoses is small. We reviewed records of brain tumor patients referred to a large tertiary referral center. We must be careful about generalizing these results to patients with brain tumor at other facilities. We tried to minimize reviewer bias by choosing standard diagnostic terms to classify erroneous or correct diagnoses. In all cases we attempted to find original documentation of patients first medical encounter following onset of neurologic symptoms, whether at JHH or another institution. In cases where we could not be certain of the original investigators assessment and impression, we classified those patients as having insufficient data.

Although we know that images were obtained on all patients before initial diagnoses were made, we do not know whether CT or MRI studies were performed. We also do not have data on whether diagnoses by emergency physicians, internists or neurologists were more accurate. Also, our presentation of data on initial presenting symptoms must be interpreted with caution. Frequently, patients presented with multiple symptoms and the study neurologist attempted to choose the most salient symptom. Our criteria for diagnosis of stroke was relatively strict. It is therefore possible that we underestimated the fraction of brain tumor patients originally suspected and evaluated for stroke.

Recognizing the shortcomings of this methodology we hope that additional research will investigate the best aids to the clinician seeing a patient with an acute neurologic deficit in the Emergency Department. If not non-contrast CT, how can we better our diagnostic discrimination between brain tumor and stroke? Walach et al. [27] found higher leukocyte alkaline phosphatase activity in patients with tumor compared to stroke patients. MRI may be a more sensitive test than CT, but at a higher cost. CT is frequently performed in the emergency department to exclude hemorrhage, a critical step in treating acute stroke patients with TPA. In most centers it is difficult to obtain 'stat' MRI scans for stroke patients and MRI may not be as good as CT in detecting acute hemorrhage. Patients with unexplained 'spells' and normal initial neuroimaging should be followed clinically and radiographically to ensure that a neoplasm is not manifest at a later time. GBM, particularly in the elderly, frequently presents clinically and is accompanied by a normal initial scan only to be followed later with an obvious tumor on repeat scan. We suggest that in stable patients who are not considered candidates for anti-coagulation or thrombolytics, delayed contrast-enhanced MRI scanning may avoid misdiagnosis and decrease the expense of performing multiple brain imaging techniques. For those patients who are candidates for thrombolytic therapy, but a suspicion for cerebral mass lesion exists, a contrast enhanced CT scan can be performed emergently to exclude tumor.

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